Stop Press - changing times

After July 2002 those of you who receive a print copy of *Bandolier* will need to do something positive if you still want to receive it. You'll have to pay for it, because NHS funding for the paper version ceases in July, and issue 101 will be the last financed and distributed as now.

Bandolier will still be here. The paper version will continue, and we will be telling individuals who can and want to pay for it how to arrange this, starting in April. Institutions in health services or non-profit organisations around the world will be able to buy in bulk and distribute themselves. Institutions interested in bulk purchase should email bandolier@pru.ox.ac.uk or fax an enquiry to 01865 226978.

The April issue will contain more information about how you can subscribe.

This issue of *Bandolier* has largely been stimulated by questions raised by patients contacting *Bandolier* after visiting its Internet resources. Readers will not be surprised that one result has been finding more information on MMR and autism. Particularly interesting is a report of a CDC-sponsored conference that included professionals and parents. It is a sensible and sensitive read. The cost of autism is huge, and parents of autistic children are surprised that we know so little about it. As professionals we perhaps get too used to our own ingnorance and should wonder at it more often.

This month there is a related issue on antiphospholipid antibodies and pregnancy loss, a relatively new topic for *Bandolier*, yet within days a new systematic review hove into sight. But there are few trials, so how do we judge when quality and size may be compromised? Some wisdom words can help. And what about all this new genetics stuff the pointy heads keep coming up with? Jargon apart, the tools we have and use now help us understand it.

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ANTIPHOSPHOLIPID ANTIBODIES AND PREGNANCY LOSS

What's worse than being asked a question to which you don't know the answer (or even understand the question)? It could be having only half of the answer, but not knowing which half. Such a position could arise with treatments for antiphospholipid antibodies in pregnancy.

Antiphospholipid antibodies are antibodies directed against several phospholipids in the body. There is an association between antiphospholipid antibodies in the circulation and pregnancy loss, and between 3% and 7% of pregnant women have the antibodies. In low risk pregnancies, the antibodies are associated with a nine-fold increase in pregnancy loss, while in high risk pregnancies with at least three previous losses, they are associated with a 90% risk of further pregnancy loss.

The mechanism of pregnancy loss is thought to be through thrombosis of placental vessels, though this is a complicated, and perhaps controversial area. The important question is whether there are effective treatments. A new systematic review [1] begins to answer that.

Systematic review

The searching strategy for this review was impressive, using the usual electronic databases, plus the Cochrane controlled trials register, plus hand-searching of specialist journals and abstracts of relevant symposia. Trials sought were those that sought to prevent pregnancy loss in pregnant women with a history of at least one previous loss and serological evidence of antiphospholipid antibodies. The primary outcome sought from the trials was pregnancy loss, though many others, including birth weight, prematurity and even issues around maternal bone mineral density were looked for.

In this issue

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Results

There were 10 randomised or quasi-randomised trials included with 627 women, and their design and results are given in detail in the review. In most trials women had at least two and often three previous miscarriages, and both treatments and the results of serology tests are described. Trials were not large, though, with 90 women being the biggest, and some were very small. Trial design was generally adequate, most being properly randomised, some blind, and with intention to treat analysis and 100% follow up in all. The biggest difficulty was the plethora of different treatments used, from aspirin alone, to heparin plus aspirin, prednisolone plus aspirin or intravenous immunoglobulin.

In direct comparisons, aspirin alone was no better than placebo or usual care, with the important qualification that these were small trials with only 70 women in total, and with what appeared to be a lowish rate of loss without treatment. Heparin and aspirin was better than aspirin in two trials with 140 patients, with a relative risk of loss of 0.45 (95% CI 0.29 to 0.70) and number needed to treat of 3.2 (2.1 to 6.3). A trial of high dose heparin versus low dose heparin, both with aspirin, showed no difference, and with rates of pregnancy loss consistent with the comparisons of heparin plus aspirin with aspirin.

A number of the trials had treatment arms that included usual care, aspirin, or heparin plus aspirin. The results in those women are shown in Figure 1 and Table 1. Heparin plus aspirin resulted in lower rates of pregnancy loss, though with wide variations in these small numbers.

Figure 1: Abacus plot of single trial arms for pregnancy loss with usual care, aspirin, and heparin plus aspirin
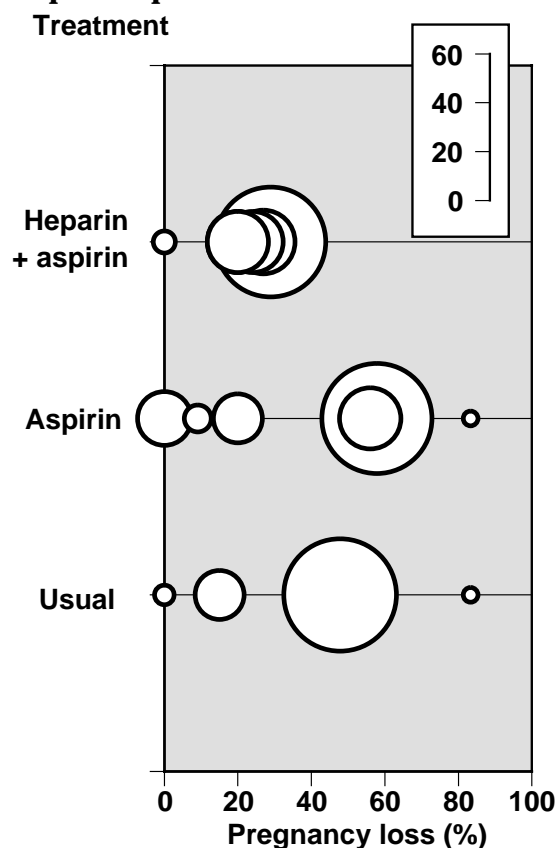

Table 1: Numbers and percentages of pregnancy losses with different treatments

Intervention	Trial arms	Losses/total pregnancies	Percent (95%CI)
None, usual care	4	30/80	37 (27 to 48)
Aspirin alone	6	50/129	39 (30 to 47)
Low MW heparin plus aspirin	6	36/155	23 (17 to 30)

One reasonably solid conclusion from other outcomes was that use of prednisolone was associated with higher rates of premature birth and admission to neonatal intensive care units. There was no evidence that it helped prevent pregnancy loss. For other treatments there were few secondary events like premature delivery, and no indication that treatment made them occur more frequently.

Comment

When a young woman asks whether any treatment is effective for recurrent pregnancy loss because of antiphospholipid antibodies, the immediate reaction for most of us will be a big question mark in a bubble coming out of our head. Last year it would have been almost impossible to answer. This year, because we now have a systematic review, it's just difficult.

In two direct comparisons, heparin and aspirin beat aspirin alone, with a NNT that we usually regard as being impressive. Looking at all trials where heparin plus aspirin, aspirin alone, or usual care have been used, heparin plus aspirin again looks a better bet. We have to acknowledge that this way of looking at available information is nothing like as conclusive as direct comparisons, but where information is scarce and numbers low, it is useful to bolster confidence in the conclusion. Prednisolone is not an option.

A more generic lesson is that we need additional confidence when numbers are low and quality uncertain, and when it is hard to judge validity becuase the territory is unfamiliar. In Figure 1, with both aspirin and usual care some trials reported no pregnancy losses while others reported more than 80% losses. Of course they were small, some treatment arms with information on as few as six women.

Clever people have looked at the uncertainties that can arise because of trial quality and trial size. The lessons for this example would be to be cautious. The trouble is that if you are a prospective mother or their professional advisor, you don't have a decade or so to wait for more or better trials to be performed. You have to make a decision now. There may be confidence in numbers and quality, but in their absence, or, as here, when they are in short supply, wisdom and experience will have to make up the deficit.

References:
1   M Empson et al. Recurrent pregnancy loss with antiphospholipid antibody: a systematic review of therapeutic trials. Obstetrics & Gynecology 2002 99: 135-144).

MINDSTRETCHER 1
– QUALITY AND SIZE

Early in the reign of Augustus, Dionysius of Halicarnasus commented that "history is philosophy from examples". We think of evidence in much the same way, in seeking examples from the archaeology of medicine to learn what constitutes good science and what bad, perhaps leavened here and there with a bit of real philosophy and science. Theory tells us that randomisation is good, and examples from reviews frequently confirm it. Yet we are condemned to relearn the lessons because so many systematic reviews include trials whose architecture potentially misleads.

And it's not just about architecture, because size is also important. Indeed, the two are linked, so some helpful revisiting of the issues of trial quality [1] and size [1,4] revivify our knowledge of these matters.

Quality and size [1]

Two Danish researchers looked for large clinical trials with at least 1,000 patients together with meta-analyses of small trials. They were asking the sensible question about how possible discrepancies between large trials and meta-analyses could be affected by methodological quality.

They found 14 meta-analyses, pulled all the original papers, subjected those to quality review, and examined outcomes in terms of odds ratios. They then used the ratio of the odds ratio in the large randomised trial to that from the meta-analysis of small trials to produce a "ratio of odds ratios" as the final outcome. When the ratio of odds ratios was significantly less than 1, that indicated that small trials with particular quality criteria exaggerated the effect of an intervention compared with the large trial.

The quality criteria they tested for were generation of the allocation sequence, allocation concealment, double blinding, and withdrawals or dropouts. The relevant criteria are in Table 1.

Table 1: Quality criteria tested

Quality feature	Adequate	Inadequate
Generation of the allocation sequence	computer-generated random number or similar	not described
Allocation concealment	central independent unit, sealed envelope, or similar	not described, or open table of random numbers
Double blinding	identical placebo or similar	not described, or tablets versus injection not double dummy
Withdrawals or dropouts	number and reasons for drop outs	not described

Results

They used 23 large trials and 167 small trials with 136,000 patients. Compared with large trials, small trials with inadequate generation or allocation concealment of the randomisation sequence, or those that were not adequately double blinded over-estimated the effect of treatment (Table 2). When methodological quality was compared in large and small trials, inadequate generation of the randomisation sequence and inadequate double-blinding caused over-estimation of the treatment effect (Table 3), and much the same was found for a similar analysis of small trials alone.

Quality scoring using the Oxford system [2], perhaps one of the most commonly used scoring systems in systematic reviews, produced sensible results. Small trials with lower quality scores over-estimated treatment effects compared with large trials. Small trials with higher quality scores did not. With both large and small trials, treatment effects were exaggerated with low versus high quality scores.

Size [3]

It is obvious that if we have a very small amount of information, from few patients, that the effects of random chance can be significant. As the amount of information or number

Table 2: Comparison of large trials with small trials with different quality criteria

Common comparator	Comparison	Ratio of odds ratios (95%CI)
Large trials	Small trials with **inadequate** generation of allocation sequence	**0.46 (0.25 to 0.83)**
Large trials	Small trials with **adequate** generation of allocation sequence	0.90 (0.47 to 1.76)
Large trials	Small trials **inadequate** allocation concealment	**0.49 (0.27 to 0.86)**
Large trials	Small trials **adequate** allocation concealment	1.01 (0.48 to 2.11)
Large trials	Small trial with **inadequate** or no double blinding	**0.52 (0.28 to 0.96)**
Large trials	Small trial with **adequate** or no double blinding	0.84 (0.43 to 1.66)
Large trials	Small trials with **inadequate** follow up	0.72 (0.30 to 1.71)
Large trials	Small trials with **adequate** follow up	0.58 (0.32 to 1.02)

When the ratio of the odds ratios is less than 1, it indicates that the feature (inadequate blinding, for example) exaggerates the intervention effect

Table 3: Comparison of adequate versus inadequate quality criteria in large and small trials

Common comparator	Comparison	Ratio of odds ratios (95%CI)
Adequate	**Inadequate** generation of allocation sequence	0.49 (0.30 to 0.81)
Adequate	**Inadequate** allocation concealment	0.60 (0.31 to 1.15)
Adequate	**Inadequate** or no double blinding	0.56 (0.33 to 0.98)
Adequate	**Inadequate** follow up	1.50 (0.80 to 2.78)

When the ratio of the odds ratios is less than 1, it indicates that the feature (inadequate blinding, for example) exaggerates the intervention effect

of patients increases, then the effects of chance will diminish. In some circumstances, like acute pain trials, we can define how much information is needed for us to be confident not just that a treatment works, but how big is the effect of that treatment [3].

Confirmation that our estimate of the effect of treatment can be heavily dependent on size comes from a study from the USA and Greece [4]. Researchers looked at 60 meta-analyses of randomised trials where there were at least five trials published in more than three different calendar years. They were in either pregnancy and perinatal medicine or myocardial infarction.

For each meta-analysis trials were chronologically ordered by publication year and cumulative meta-analysis performed to arrive at a pooled odds ratio at the end of each calendar year. The relative change in treatment effect was calculated for each successive additional calendar year by dividing the odds ratio of the new assessment with more patients by the odds ratio of the previous assessment with fewer patients. This gives a "relative odds ratio", in which a number greater than 1 indicated more treatment effect, and one less than 1 indicates less treatment effect.

The relative odds ratio can be plotted against the number of patients included. The expected result is a horizontal funnel, with less change with more patients, and the relative odds ratio settling down to 1.

Results

In the paper, the two graphs for pregnancy/perinatal medicine and myocardial infarction showed exactly this expected

pattern, but are just impossible to reproduce here. Below 100 patients the relative odds ratios varied between 0.2 and 6. By the time 1000 patients were included they were between 0.5 and 2. By 5,000 patients they settle down close to 1. The 95% prediction interval for the relative change in the odds ratio for different numbers for both examples is shown in Table 4.

When evidence was based on only a few patients there was substantial uncertainty about how much the pooled treatment effect will change in the future. With only 100 patients randomised, additional information from more trials could multiply or divide the odds ratios at that point by three.

Comment

At first look this is all complicated pointy-head stuff, but actually it's no more than simple common sense. If trials are not done properly, they might be wrong. If trials are small, they might be wrong. To be sure of what we know we need large data sets of high quality, whether from single trials or meta-analyses. The corollary is that if we have small amounts of information, or information of poor quality, the chance of that result being incorrect is substantial, and then we need to be cautious and conservative.

Cynics might say that much decision-making in healthcare is done on small amounts of inadequate information. They may be right, but knowing that that information may be misleading is still helpful, because we know that we need to examine what we do in practice to check that it conforms with what we thought we started out with. Suspending belief is not an option.

References:
1   LL Kjaergard & C Gluud. Reported methodologic quality and discrepancies between large and small randomised trials in meta-analyses. Annals of Internal Medicine 2001 135: 982-989.
2   AR Jadad et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled Clinical Trials 1996 17: 1-12.
3   RA Moore et al. Size is everything - large amounts of information are needed to overcome random effects in estimating direction and magnitude of treatment effects. Pain 1998 78: 209-16.
4   JP Ioannidis & J Lau. Evolution of treatment effects over time: empirical insight from recursive metaanlyses. Proceedings of the National Academy of Sciences 2001 98: 831-836.

Table 4: 95% prediction interval for relative change in odds ratio for different numbers of accumulated patients randomised

Number of patients	Fixed effect prediction interval for relative change in odds ratio	
	Pregnancy/perinatal	Myocardial infarction
100	0.32 - 2.78	0.18 - 5.51
500	0.59 - 1.71	0.60 - 1.67
1000	0.67 - 1.49	0.74 - 1.35
2000	0.74 - 1.35	0.83 - 1.21
15000	0.85 - 1.14	0.96 - 1.05

Mindstretcher 2
– genetics and disease

One of the most unsettling lectures we listen to is given by someone ("pointy-headed academic" is a favourite description of *Bandolier* readers) who tells us of the changes to be wrought by the tidal wave of new genetic knowledge coming our way. Most of us feel the correct response is to "do an Ostrich" (bury your head in the sand) and hope we retire before this all comes to pass. Too late, because the questions, and some of the answers, may already be upon us.

But there is hope, and part of that hope is that dealing with genetic knowledge may not be so different from dealing with other forms of knowledge. We can cope as long as we are not overawed by the jargon. Two examples are helpful, one on factor V Leiden and the risk of thrombosis [1], the other a study and meta-analysis of the relationship between ACE gene polymorphism and IgA nephropathy [2].

Factor V Leiden

This gene mutation is associated with resistance to activated protein C, a natural anticoagulant and inhibitor of the coagulation system. The mutation can be found in a significant minority of people with documented venous thrombosis, and there is a three to seven-fold increased risk of venous thrombosis in heterozygous carriers of the gene mutation.

This has led to some consideration for screening for factor V Leiden mutation. The problem with this is that we have only limited knowledge of the natural history of thrombosis in people with the mutation, which makes it difficult to balance any benefits of anticoagulation therapy following gene identification with the risks associated with anticoagulation therapy.

Study

A Dutch study [1] helps by looking at the natural history in a large population of gene carriers. In all 470 asymptomatic carriers (458 heterozygotes and 12 homozygotes for the gene mutation, mean age 43 years) who were first-degree relatives of symptomatic patients were followed every six months for an average of 3.3 years, with a range of 1.5 to 4.5 years. People with a history of thromboembolism or on long-term anticoagulation therapy were excluded. Nine withdrew for various reasons and three died, but none developed venous thromboembolism. Thromboembolism was diagnosed appropriately if clinically suspected.

Results

Nine heterozygous carriers had a venous thromboembolism. Four occurred spontaneously, three were associated with use of oral contraceptives (66 women used oral contraceptives), one with hormone replacement therapy (21 women used hormone replacement therapy) and one after surgery despite one week of anticoagulation (29 people had surgery). None occurred in 17 pregnancies.

The overall absolute rate of venous thromboembolism was 0.6% a year (95% CI 0.3% to 1.1%), consistent with smaller studies. This was higher than reported rates in populations free of the mutation, in which it is reported to be about 0.2%.

Comment

If screening and identification of factor V Leiden mutation resulted in warfarin anticoagulation, intracranial haemorrhage might occur in about 0.5% of treated patients and major bleeding in up to 3% every year, though these figures (see *Bandolier* Internet site) were from older populations. The paper [1] quotes major bleeding with warfarin of 2% to 10% a year. Whatever, the benefits and harms are not importantly balanced towards benefit. Where there are more risks, like surgery or contraception, other criteria may apply, and the paper is thoughtful about them.

ACE gene polymorphism

IgA nephropathy leads to end stage renal disease, more often in men, at older age, and in the presence of hypertension and proteinuria. The angiotensin converting enzyme comes in three genotypes, DD, II and DI. Some small studies have shown high rates of the DD form of ACE in IgA nephropathy patients with progressive deterioration of renal function.

Problems were that the frequency of different genotypes in different populations varied, as well as the small numbers. A large study in a homogenous population plus a meta-analysis of such studies [2] helps answer the question.

Study

The study population was 247 Caucasian patients in Southern Italy with IgA nephropathy diagnosed by renal biopsy and visited the clinic within three years. Two outcomes of renal disease progression were used, either progression of renal damage using creatinine clearance or development of end-stage renal disease treated by dialysis or transplantation. A control population was 140 staff members and blood donors. In addition an extensive search was made for other studies relating to ACE gene polymorphism and renal damage.

Results

In the study, there was no relationship between ACE I/D genotype and renal damage. In the meta-analysis, studies were divided between those in Asians and in Caucasians, because of different genotype frequencies in controls. There was no association between ACE I/D frequencies and IgA nephropathy or progression of renal damage in IgA nephropathy patients.

Comment

A mind-tinglingly complex paper, but one that dissects the problems, examines the answers, and comes up with a probably conclusive lack of relationship.

Overall comment

It might be easy to be put off by these papers, especially when they get into the details of the gene sequences used to identify genotypes, or the unfamiliar notations used in genetics. But genetics aside, the *methods* used were familiar, and similar to those we are used to from other papers we read. A little stamina meant we found a satisfactory answer, that in neither case do we have to worry about these any more for the moment, though factor V Leiden may be relevant in some situations.

The future may be more challenging. *Bandolier* hopes that transmission disequilibrium tests that are free of bias due to population stratification can wait till brain cells have a good day.

References:
1   S Middeldorp et al. A prospective study of symptomatic carriers of the factor V Leiden mutation to determine the incidence of venous thromboembolism. Annals of Internal Medicine 2001 135: 322-327.
2   FP Schena et al. ACE gene polymorphism and IgA neph-ropathy: an ethnically homogeneous study and a meta-analysis. Kidney International 2001 60: 732-740.

MEASLES VACCINATION SCHEDULES

In areas without recurrent measles transmission WHO recommends the first dose of measles immunisation is MMR at 12-15 months of age. In areas where there is recurrent measles transmission, a two-dose schedule is used with a monovalent vaccine given at nine months, followed by MMR at 15 months. Timing is important as maternal transplacental antibodies decline and infants face an unprotected gap before immunisation. Early protection might be beneficial where measles is more common. A randomised trial in Turkey examined the efficacy of the two approaches.

Trial

The subjects were 1000 healthy infants aged nine months in five different centres in Ankara. Those with no known history of chronic disease, like immunodeficiency, asthma, or atopy were included. Infants were randomly allocated to receive monovalent measles vaccine (MV) at nine months followed by MMR at 15 months (MV/MMR group) or MMR at 12 months (MMR group).

Blood samples were collected for serology before vaccination, and six weeks after MMR vaccination. Midwives visited children at home several times up to one month after vaccination to collect adverse reaction records made by parents. Families were followed up by telephone every three months for five years using a standard questionnaire. Measles infection in children was actively sought, and diagnosed clinically and serologically.

Results

The MV/MMR group had 58 withdrawals, 50 because a different batch of vaccine was used, four through immigration (sic) and four because of withdrawal of consent. In the MMR group there were five withdrawals, one through immigration (sic) and four withdrawals of consent.

Before vaccination, MV/MMR infants had higher antibody titres than MMR infants, reflecting their younger age at vaccination. Six weeks after the MMR vaccination, measles antibody titres were higher in children in the MMR group (Figure 1). The proportion of children with adequate levels of antibodies after MMR vaccination was similar for mumps and rubella, but significantly lower (at 70%) in MV/MMR infants than in MMR infants (90%) (Figure 2).

Figure 1: Measles antibody titres in infants before vaccination and six weeks after the MMR vaccination
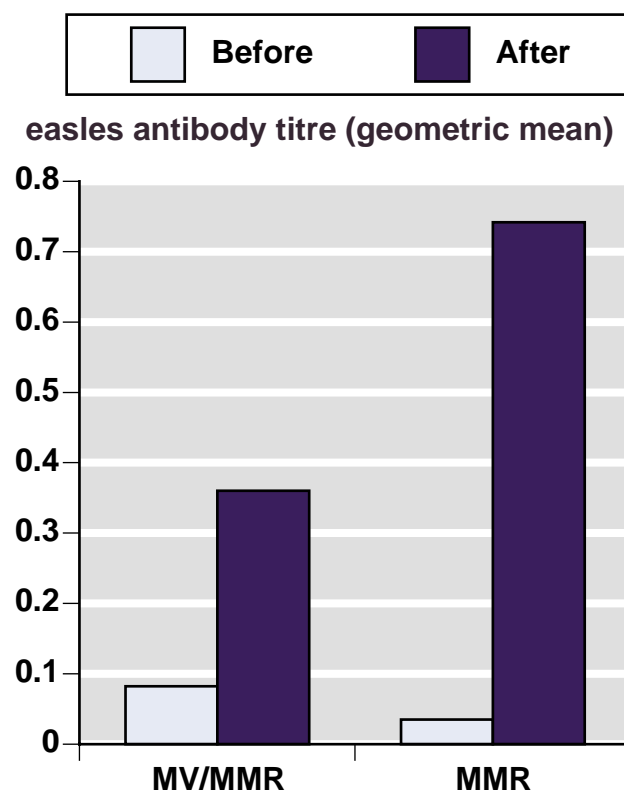

Episodes of fever, cough, rash, diarrhoea, and local redness and swelling were similar in incidence between the two groups, though runny nose was more common at 4% after MMR in the MMR group.

Twelve children acquired measles in the follow up period, all at 12-36 months of age, and all in the MV/MMR group. Cases were scattered between the five centres, with no known epidemiological link. None was serious and none required hospital admission.

Comment

This study was interesting for a number of reasons. It tested a WHO recommendation that has major implications in

Figure 2: Percentages of infants with adequate antibody titres suggesting protection against measles, mumps and rubella six weeks after the MMR vaccination
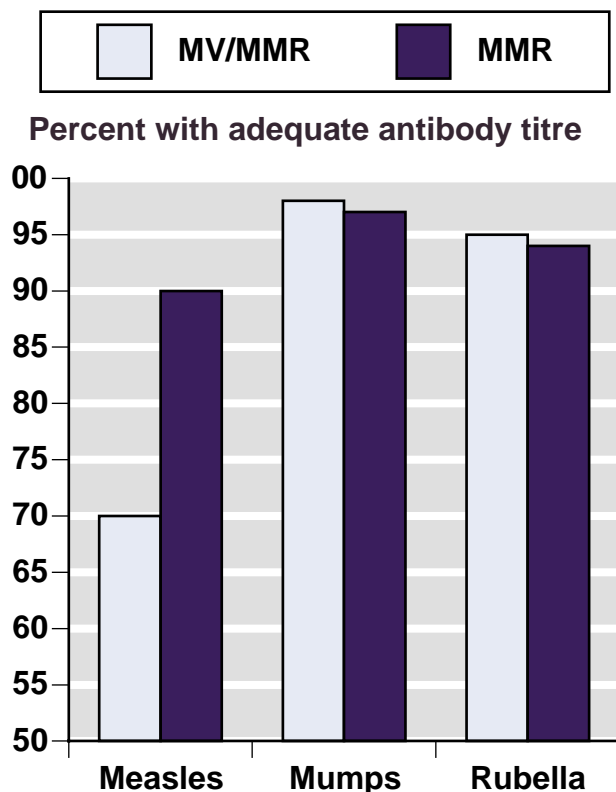
parts of the world where measles continues to be an important cause of morbidity and mortality, as in Turkey. The results question the timing and structure of vaccination.

They are also important for countries like the UK where vaccine uptake can be below ideal in some areas. The study could be seen as casting doubt on the reliability of some vaccines other than MMR. A 70% protection rate in MV/MMR children is underwhelming, though this should not be extrapolated to possible results for monovalent measles vaccines given in different regimens in places where measles is not endemic (though that is not the WHO recommendation).

Finally it reminds us that what is true of the UK, Europe or North America is not always true of the rest of the world. Taking unvaccinated children on hols to Turkey or other parts where measles is endemic puts them at significant risk either as small children or later in life. The unvaccinated infant is also an unvaccinated teenager and student. Children grow up, and increasingly they travel. Folk who doubt the importance or severity of measles, especially in the developing world, could do worse than refresh their memories with a quick dip into the Oxford Textbook of Medicine. It is not a fun read.

References:

1   M Ceyhan et al. Immunogenicity and efficacy of one dose measles-mumps-rubella (MMR) vaccine at twelve months of age as compared to monovalent measles vaccination at nine months followed by MMR vaccination at fifteen months of age. Vaccine 2001 19: 4473-4478.

MMR AND AUTISM – US CONFERENCE

Britain these past few weeks has seen an unprecedented spate of media-inspired hype over the safety of MMR. Some people give us their views, others present the facts, and a presenter then tells us they can't make sense of it all. That's a pity, because there's a lot of sense to be made. Right now there's far too much heat and not enough light.

So for some calm reflection and good common sense from doctors, scientists, parents and government, let's cross the pond to the USA and see how these things might be handled better. In June 2000, sponsored by the Centres for Disease Control and Prevention, the American Academy of Pediatrics convened a conference on "New challenges in childhood immunizations" in Illinois. The conference was attended by representatives from various paediatric committees, parents, practitioners and scientists, with a multidisciplinary panel of experts to review the evidence on what was known about the pathogenesis, epidemiology and genetics of autistic spectrum disorders, and what was known about the supposed link between inflammatory bowel disease, measles and MMR vaccine.

The report [1] can be downloaded from the Pediatrics website, and the URL is given below. It is 23 pages long, but worth every word. It is comprehensive and authoritative, yet humble and sensitive at the same time. Some of the results and conclusions are in Table 1. The paper looks at every aspect of the autism and measles vaccination, and especially the link with MMR. The application of causality criteria is particularly useful, and there is a voluminous reference list.

In particular, it calls for more and better research to understand and prevent autistic spectrum disorders and identifies areas for further study, including:

Table 1:

Main results of US conference on MMR and autism

Autism is a complex disorder of uncertain and probably multiple aetiologies.

Abnormal brain development in autism may occur before 30 weeks' gestation.

In utero, rubella is a known cause of autism.

Animal data support the biological plausibility that exposure to unrecognised infectious or environmental agents could cause autistic spectrum disorders.

Increased reporting of autistic spectrum disorders occurred long after the introduction of widespread use of MMR vaccine in the USA in 1971.

Some children with autistic spectrum disorders have gastrointestinal symptoms, but an increased rate has not been established.

Separate administration of measles mumps and rubella vaccines provides no benefit over MMR and would result in delayed or missed immunisations.

Continued scientific efforts need to be directed to the identification of causes of autistic spectrum disorders.

- Factors associated with autistic spectrum disorders, including genetics and environmental exposures in utero and during the first months of life.
- The nature and incidence of regression in autistic spectrum disorders.
- Epidemiological studies to determine whether there are changes in the incidence and prevalence of autism, and to identify risk factors.
- Whether measles or other viruses persist after infection or immunisation.
- Factors responsible for differences in immunologic parameters in people with autistic spectrum disorders and those unaffected.
- Whether there is evidence for previously unrecognised infectious agents affecting the central nervous system of persons with autistic spectrum disorders.

Reading and understanding this paper would greatly benefit healthcare professionals dealing with childhood vaccinations. It's language is accessible for parents as well. It may not be the easiest of reads for any of us, but all of us can benefit from it. There's also more on the CDC Internet site at www.cdc.gov/nip/vacsafe/concerns/autism/.

Perhaps the most important lesson from the conference is that it is less about proving the lack of a link between MMR and autism, and more about finding the cause of autism and doing something about it.

And the secondary lesson is that involving the public in difficult decisions is not only impossible, but actually beneficial. One of the most impressive things about this paper is it's language and tone, written for worried parents as well as busy policy makers.

References:
1   NA Halsey et al. Measles-mumps-rubella vaccine and autistic spectrum disorder: a report from the New Challenges in Childhood Immunizations conference convened in Oak Brook, Illinois, June 12-13, 2000. Pediatrics 2000 107. (www.pediatrics.org/cgi/content/full/107/5/e84)

COST OF AUTISM IN BRITAIN

Autism is important because it condemns children to a lifetime of difference. Right now we don't know the cause, nor do we have any effective remedies. That will change, and at some point decisions will need to be made not only about the effectiveness of any preventive measures or treatments, but also about their cost-effectiveness.

That entails knowing something about the costs of autism. A new study from the Institute of Psychiatry gives us an informed insight [1]. The bottom line is that the cost of autism in Britain is of the order of £1 billion.

Study

The authors performed systematic searches of literature, of various electronic databases, and contacted authors and experts to assemble the package of information on the disorder, its impact on individuals, families and society, and on the costs involved. At each stage of the cost calculations the evidence is outlined in detail.

Results

The main results are shown in Table 1. For a person with autism and additional learning disability the average lifetime costs was £2.94 million. For someone with higher functioning autism the average lifetime cost is £785,000. With an assumed prevalence of autism of five per 10,000 and with 75% of persons with autism having additional learning disability, the annual social cost of autism in Britain is £957 million.

Comment

This study will be particularly useful in assessing the cost effectiveness of prevention strategies or treatment strategies in future. In the meantime it is a wake up call about the seriousness of autism in financial as well as human terms.

References:
1   K Järbrink & M Knapp. The economic impact of autism in Britain. Autism 2001 5: 7-22.

Table 1: Costs of autism in Britain for individuals (lifetime) and society (annual)

Cost category	Individual with learning disability (£)	Individual with higher functioning autism (£)	UK total (£ million)
Hospital services	26,600	30,700	11
Medication	3,400	8,300	2
Other health and social servcies	71,600	31,200	25
Living support	2,134,000	312,500	669
Voluntary support	18,800	----	5
Special education	179,100	108,300	64
Sheltered work	16,200	67,800	12
Day activities	422,400	74,500	134
Lost productivity	---	137,100	14
Family members time	39,600	14,400	13
Family expenses	30,800	---	9
Total	**2,940,500**	**784,800**	**957**